

BMJ Open Vitamin D supplementation and energy and metabolic homeostasis in obese and overweight subjects: a protocol for a systematic review

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ABSTRACT

Introduction Obesity and vitamin D deficiency are major public health problems. According to the pathophysiological mechanism of obesity as well as the bidirectional relationship between obesity and vitamin D metabolism and storage, vitamin D supplementation in obese and overweight subjects could have beneficial effects on the energy and metabolic homeostasis. This review will assess the efficacy of vitamin D supplementation on the energy and metabolic homeostasis in overweight and obese subjects.

Methods and analysis In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, we retrieved the relevant literature from the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE and the Cochrane Central Register of Controlled Trials, from inception to June 2021. A manual search of the reference lists of all the relevant research articles will be performed to identify additional studies. We will include randomised controlled trials (RCTs) published in English that examine the effects of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. RCTs with multiple vitamin D groups will also be included. Two reviewers will independently complete the article selection, data extraction and rating. The bias tool from the Cochrane Handbook for Systematic Reviews of Interventions was used to assess the methodological quality of the included studies. A narrative or quantitative synthesis will be performed based on the available data. The planned start and end dates for the study were 1 February 2021 and 1 March 2022.

Ethics and dissemination Ethical approval will not be required for this review. The results of this review will be disseminated in a peer-reviewed journal.

PROSPERO registration number CRD42021228981.

INTRODUCTION

The definition of overweight and obesity is abnormal or excessive fat accumulation that may impair health.¹ With the continued increase in the prevalence worldwide, overweight and obesity have been described as a global pandemic.^{2–5} Since 1975, the worldwide prevalence of obesity has nearly tripled.¹ In 2016, over one-third of adults worldwide

Strengths and limitations of this study

- The study will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and recommendations of the Cochrane handbook, which are well-recognised approaches for conducting and reporting of systematic reviews.
- Two reviewers will independently complete the article selection, data extraction and rating, and possible disagreements will be resolved by discussion or consultation with a third author.
- Different protocols for vitamin D supplementation may lead to a large degree of heterogeneity.
- If applicable, prespecified subgroup analyses will be conducted to exclude the differences related to the vitamin D supplementation protocol, comorbid condition or age group.
- When possible, sensitivity analyses will be conducted to test whether the conclusions are robust.

were overweight and 13% were obese^{1 6}; over 340 million children and adolescents aged above 5 years were overweight or obese.^{1 6} If this trend continues, it has been projected that up to 57.8% of the world's adult population could be either overweight or obese by 2030.⁷ The high prevalence of overweight and obesity, combined with the associated disease burden as well as higher all-cause mortality makes it a global public health challenge.^{8 9} Moreover, the disease burden of overweight and obesity has been greatly magnified by the current COVID-19 pandemic, as overweight and obesity were represented as an unfavourable factor for COVID-19 severity and mortality.^{10–12}

Vitamin D deficiency is another important public health issue, which often coexists with obesity.^{13 14} The inverse association between the body mass index (BMI) and vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentration) has been suggested irrespective of age, sex, latitude, population group

or cut-offs to define vitamin D deficiency,^{13 15 16} which may be related to a bidirectional relationship between the adipose tissue and vitamin D metabolism, storage and action.^{17–23} Obesity has been shown to involve a chronic state of low-grade inflammation that dysregulates glucose, lipid and energy metabolism, termed metaflammation.^{24–26} In addition to the metabolic dysregulation in the major peripheral organs that control the energy flux,²⁷ metaflammation disturbs the brain function, especially affecting the brain areas that regulate energy and metabolic homeostasis, such as the hypothalamus.^{28–32} It has been suggested that vitamin D could play a role in anti-obesity, which at least was partly mediated by the vitamin D receptor in the adipocytes/peripheral organs^{33–36} and the brain.^{36–38} Thus, this has given rise to the hypothesis that vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

The assessment of vitamin D supplementation in obese and overweight subjects has been gaining increasing attention in recent randomised clinical trials (RCTs). Several earlier reviews and meta-analyses of RCTs have examined the effect of vitamin D supplementation on weight loss, serum vitamin D concentration and inflammatory or glycaemic markers in overweight and obese individuals with or without comorbid conditions, with limited and less conclusive results.^{13 33 39–45} However, the energy and metabolic homeostasis-related biomarkers have not been clearly and fully investigated in the above studies. Therefore, we sought to undertake a comprehensive systematic review of RCTs to evaluate the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

METHODS

Study registration

This protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).⁴⁶ The final study was developed in accordance with the PRISMA statement,⁴⁷ under the guidance of the Cochrane Handbook for Systematic Reviews of Interventions.⁴⁸

Inclusion criteria for study selection

Studies will be included for review if they meet the following inclusion criteria:

Participants

The adult participants were defined as being overweight or obese (BMI ≥ 25 kg/m² (overweight), BMI ≥ 30 kg/m² (obese)).⁴⁹ No restrictions will be assigned with regard to the sex, race, geographical distribution and diseases of the participants enrolled in the study.

Intervention

Participants in the experimental group were treated with vitamin D supplementation. Any vitamin D and its

analogue supplementation will be qualified. There will be no limitations on the routes of administration (oral or intramuscular), dose and duration.

Comparison

No vitamin D supplementation under the same treatment programme, placebo or sham control.

Outcome measures

Primary outcomes: The energy metabolism outcomes, such as the total energy expenditure, resting metabolic rate, resting energy expenditure, basal and maximal oxygen consumption rate, bioenergetic health index (BHI), glucose and lipid metabolism outcomes, such as the fasting plasma concentration of glucose and insulin, homeostasis model assessment for insulin resistance (HOMA), HOMA for β -cell function, glycated haemoglobin, lipid (cholesterol and triglycerides) profiles and plasma levels of adipokines (adiponectin and leptin). The secondary outcomes included anthropometric and body composition parameters, such as height, weight, waist to hip ratio, BMI, fat mass, fat-free mass, serum 25(OH)D concentration and adverse events.

Study design and language

We will include only RCTs published in English.

Studies will be excluded if they were quasi-randomised trials and other types of studies, reported in books, conference proceedings, dissertations or did not have available data for analysis.

Search methods for the identification of studies

We will retrieve relevant literature across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE and Cochrane Central Register of Controlled Trials, from inception to June 2021. A search will be conducted using a combination of medical subject heading (MeSH) terms, free-text words and Boolean operators. The concepts of 'participants', 'intervention' and 'RCTs' will be combined with the 'AND' operator. The participants will be defined as overweight and obese subjects, and the intervention is defined as vitamin D supplementation. For each concept, we will combine synonyms and MeSH terms with the 'OR' operator. We will be developing a search strategy for MEDLINE via Ovid (see online supplemental material appendix 1-Search Strategy Example) and adapt this strategy for the other databases. A manual search of the reference lists of all the relevant research articles will be performed to identify additional studies.

Data collection

Study selection

The bibliographic software Endnote (V.X7) will be used to store, organise and manage all the references. After the removal of duplicate articles, the titles, abstracts and keywords of the retrieved articles will be screened independently by two authors (NS and YH) with predefined criteria to identify the eligible studies. After preliminary

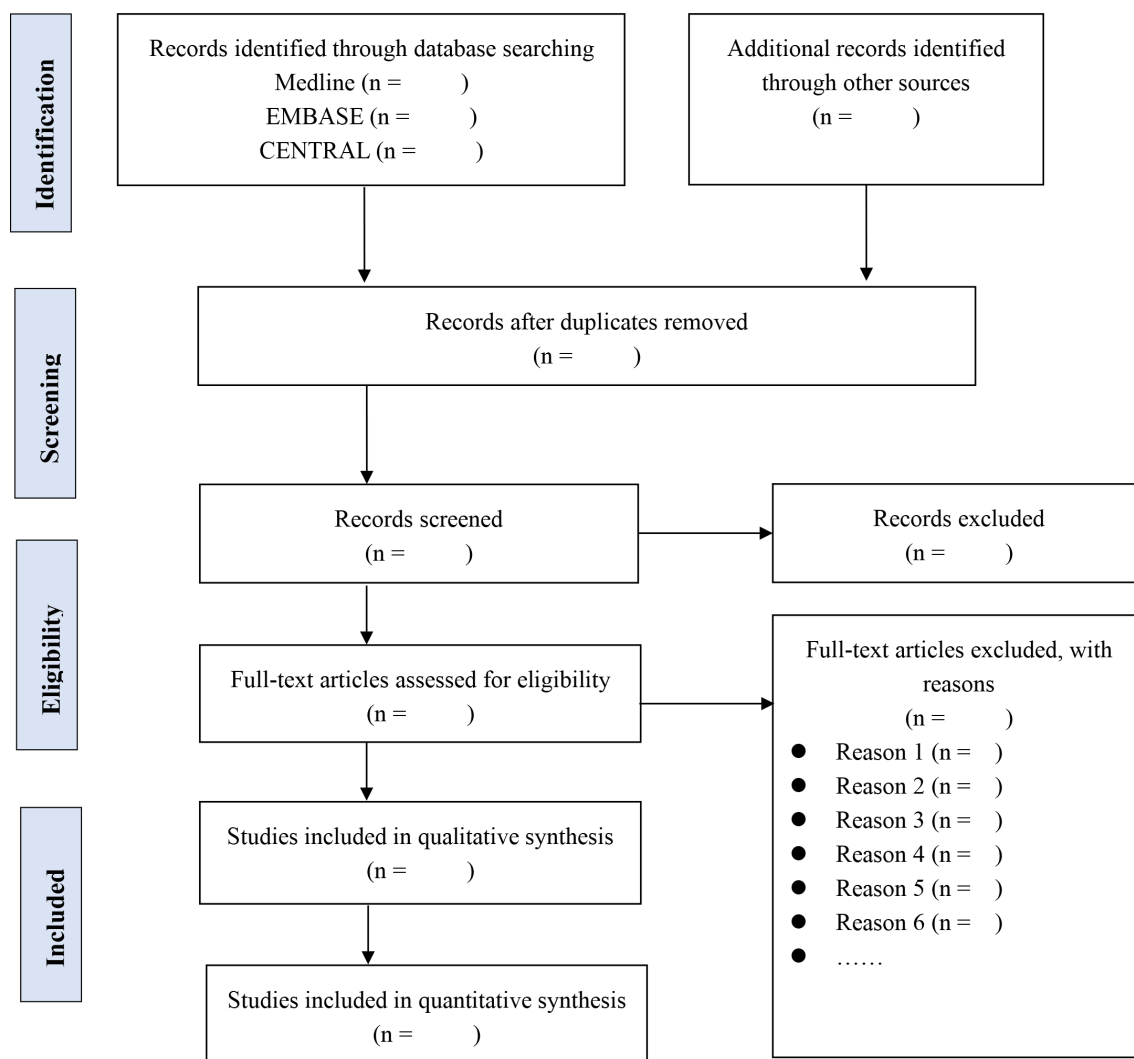


Figure 1 Flow chart of the study selection procedure. CENTRAL, Cochrane Central Register of Controlled Trials.

screening, we will review the full text of potentially eligible articles in detail, to further assess the eligibility, and the reasons for exclusion will be recorded. Any disagreement between the two review authors will be resolved by discussion or consultation with a third author. The final selection procedure will be following the PRISMA guidelines,⁴⁷ and is presented in figure 1.

Data extraction and management

Two authors (NS and YH) will independently extract the relevant data from the selected studies using a predefined data acquisition form. The extracted data will include the following items:

1. General information: The first author, title, journal, publication year, country, study setting, ethical approval, trial registration and the funding source.
2. Trial characteristics: study design, method of randomisation, allocation concealment, incomplete outcome data and blinding (participants, researchers and outcome assessors).
3. Intervention: intervention (type, form, dose and duration of vitamin D supplement provided) and comparison

intervention (form, dose, and duration of placebo provided).

4. Participants: Participant demographics, baseline characteristics, inclusion/exclusion criteria, total number and number in each group, and the assessment of compliance and withdrawals.
5. Outcomes and related information: primary and other outcomes, adverse events, duration of follow-up, and intention-to-treat (ITT) analysis.

Possible discrepancies will be resolved through discussion or consultation with a third author. If necessary, we may also contact the original authors for additional relevant information.

Assessment of risk of bias in included studies

This review will use the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions as the methodological criteria.⁴⁸ The risk of bias for the selected trials will be independently assessed by two authors (NS and YH) based on the following criteria: random sequence generation, allocation concealment, blinding of participants, researchers and outcome assessors, incomplete

outcome data, selective reporting and other sources of bias. The trials will be rated as low risk, unclear risk or high risk, or in each domain after evaluation. Possible disagreements will be resolved through discussion or consultation with a third author.

Data analysis and synthesis

The Cochrane Review Manager software (V.5.3) will be used for the meta-analysis. In our study, a meta-analysis concerning the effects of vitamin D supplementation will be conducted if two or more studies used the same outcome measure or measured similar constructs.

The summary results are computed in different ways by the data type. Continuous data will be analysed using standardised mean differences with 95% CI, while the OR with 95% CI will be computed to analyse the dichotomous data.

Heterogeneity across the studies will be analysed using the χ^2 test and I^2 statistic.^{48 50} If $p>0.1$, $I^2<50\%$, a fixed effects model will be used; if $p>0.1$, $I^2\geq 50\%$, a random effects model will be used, substantial heterogeneity is considered in this case; if $p\leq 0.1$, statistical significance is considered, and a subgroup analysis or a narrative description will be carried out.⁴⁸

If applicable, prespecified subgroups will be conducted to explore factors that might impact the strength of the effect, such as the type of vitamin D supplement; form of vitamin D supplement; whether a comorbid condition exists or not and the age group.⁴⁸

When possible, we will perform sensitivity analyses on the following factors to explore the influence of the study quality on the outcomes, such as allocation concealment, blinding of the outcome assessors, drop-out and ITT analysis.⁴⁸

If more than ten trials are included in a result of a meta-analysis, a funnel plot will be constructed to assess the potential publication bias.⁴⁸

The quality of the evidence will be evaluated using GRADEpro software (V.3) at four levels (high, moderate, low or very low) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.⁵¹ Two authors (NS and YH) will evaluate the quality of the evidence using GRADE, and possible discrepancies will be resolved through discussion or consultation with a third author.

Patient and public involvement

This systematic review protocol does not directly involve patients or the general public. The data will be collected from published articles retrieved from the main databases and manual searches.

Ethics and dissemination

Ethical approval will not be required for the performance of this review protocol. The results of this research will be disseminated in a peer-reviewed journal.

DISCUSSION

This protocol was registered prospectively in PROSPERO and developed in accordance with the PRISMA-P.

This review systematically and comprehensively assessed the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. This review protocol provides an overview of the current situation in this area, and we hope that this study will be helpful in providing a valuable reference for future evidence-based and fundamental research to refine vitamin D supplementation in clinical practice and public health.

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Contributors NS, YH and AZ contributed to the conception and design of the study. NS registered the protocol in the PROSPERO database. YH drafted the protocol. NS and AZ revised the protocol critically for important intellectual content. ML and XY designed the search strategy. NS, YH, AZ, ML and XY participated in the design of data acquisition, analysis and interpretation. All authors have read and approved the final protocol. NS is the guarantor of the protocol and the final review.

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Appendix 1

Search Strategy Example: MEDLINE (via Ovid) search

Terms specific to vitamin D

#1 exp Vitamin D/

#2 (Vitamin D OR Vitamin D2 OR Vitamin D3 OR Cholecalciferol* OR Calciol OR Hydroxycholecalciferol* OR Hydroxyvitamin* D OR Calcitriol OR Calcidiol OR Calderol OR Calcifediol OR Hydroxycholecalciferol OR Dedrogyl OR Hidroferol OR Ergocalciferol* OR Calciferol* OR Ercalcidiol OR Hydroxycalciferol OR Dihydratachysterol OR Tachystin OR Dihydratachysterin OR Calcamine OR Alphacalcidol OR alfacalcidol). ab,ti.

#3 #1 OR #2

Terms specific to overweight and obesity

#4 exp overweight/

#5 exp obesity/

#6 exp adiposity/

#7 (overweight* OR over weight* OR obes* OR adipos* OR fat). ab,ti.

#8 #4 OR #5 OR #6 OR #7

Terms for identifying randomized controlled trials

#9 exp randomized controlled trial/

#10 randomized controlled trial.pt.

#11 controlled clinical trial.pt.

#12 (random* OR placebo OR sham OR trial OR groups). ab,ti.

#13 #9 OR #10 OR #11 OR #12

Combination of terms to identify randomized controlled trials of vitamin D for obese and overweight subjects

#3 AND #8 AND #13